

9/18/06

L9 ANSWER 1 OF 14 BIOSIS COPYRIGHT (c) 2006 The Thomson Corporation on STN  
AN 2003:326802 BIOSIS  
DN PREV200300326802  
TI THE CANNABINOID LIGAND AM251 ACTS As AN INVERSE AGONIST AT THE CB1  
RECEPTOR IN VITRO, AND INDUCES WEIGHT LOSS IN CAFETERIA DIET - FED MICE IN  
VIVO.  
AU Hjorth, S. [Reprint Author]; Johansson, M. S. [Reprint Author]; Carlsson,  
K.; Greasley, P. J.  
CS Integrative Pharmacology, AstraZeneca R and D, Molndal, Molndal, Sweden  
SO Society for Neuroscience Abstract Viewer and Itinerary Planner, (2002)  
Vol. 2002, pp. Abstract No. 775.17. <http://sfn.scholarone.com>. cd-rom.  
Meeting Info.: 32nd Annual Meeting of the Society for Neuroscience.  
Orlando, Florida, USA. November 02-07, 2002. Society for Neuroscience.  
DT Conference; (Meeting)  
Conference; (Meeting Poster)  
Conference; Abstract; (Meeting Abstract)  
LA English  
ED Entered STN: 16 Jul 2003  
Last Updated on STN: 16 Jul 2003  
AB AM251 is a close structural (4-iodophenyl) analogue to the reference CB1  
receptor inverse agonist SR141716 and is frequently used as an antagonist  
at the CB1 sites. The present study assessed i) whether the drug is  
indeed a true CB1 receptor antagonist and, given central CB1 receptor  
modulation of food intake, ii) if its sub-chronic administration would  
induce weight loss in obese mice. AM251 was compared with  
SR141716 with regard to its ability to inhibit GTPgammaS binding mediated  
by CB1 receptors expressed in HEK293 cells in vitro, and to reduce body  
weight in cafeteria diet-fed mice. AM251 was approximately 3x less potent  
than SR141716 (IC50 6.4 and 1.8 nM, respectively) in the GTPgammaS assay,  
and both agents demonstrated equivalent inverse agonist properties. In  
vivo, 7 days administration of AM251 or SR141716 (10mg/kg i.p. once daily)  
resulted in a significant drop in body weight of about 8% from baseline  
(despite continued access to palatable diet). The response to both  
compounds in this regard was virtually superimposable. For comparison,  
untreated and vehicle animals gained approx 5% weight over the same time  
period. We conclude that AM251 is not an antagonist but rather an inverse  
agonist at CB1 receptors, displaying slightly lower potency than, but  
similar efficacy to SR141716. Moreover, both agents induced clear-cut  
weight loss in cafeteria diet-induced obese mice, thus  
concurring with the notion that inverse agonism at (central) CB1 receptors  
affects appetite and/or reward mechanisms and may represent an important  
exploitable target in the development of novel anti-obesity  
treatments.  
AB. . . antagonist and, given central CB1 receptor modulation of food  
intake, ii) if its sub-chronic administration would induce weight loss in  
obese mice. AM251 was compared with SR141716 with regard to its  
ability to inhibit GTPgammaS binding mediated by CB1 receptors expressed.  
. . . displaying slightly lower potency than, but similar efficacy to  
SR141716. Moreover, both agents induced clear-cut weight loss in  
cafeteria diet-induced obese mice, thus concurring with the  
notion that inverse agonism at (central) CB1 receptors affects appetite  
and/or reward mechanisms and may represent an important exploitable target  
in the development of novel anti-obesity treatments.  
IT Major Concepts  
Behavior; Nutrition; Pharmacology  
IT Diseases  
obesity: nutritional disease  
Obesity (MeSH)  
IT Chemicals & Biochemicals  
AM251: anorexic-drug, cannabinoid ligand; CB1 receptor; SR14176  
RN 51709-03-6Q (AM251)  
183232-66-8Q (AM251)

L9 ANSWER 2 OF 14 BIOSIS COPYRIGHT (c) 2006 The Thomson Corporation on STN  
 AN 2003:326801 BIOSIS  
 DN PREV200300326801  
 TI VOLUNTARY EXERCISE FACILITATES THE EFFECTS OF AM251 ON BODY WEIGHT LOSS IN  
 GENETICALLY OBESE AND WILDTYPE MICE.  
 AU Zhou, D. [Reprint Author]; Shearman, L. P. [Reprint Author]  
 CS Department of Pharmacology, Merck Research Laboratories, Rahway, NJ, USA  
 SO Society for Neuroscience Abstract Viewer and Itinerary Planner, (2002)  
 Vol. 2002, pp. Abstract No. 775.16. <http://sfn.scholarone.com>. cd-rom.  
 Meeting Info.: 32nd Annual Meeting of the Society for Neuroscience.  
 Orlando, Florida, USA. November 02-07, 2002. Society for Neuroscience.  
 DT Conference; (Meeting)  
 Conference; Abstract; (Meeting Abstract)  
 Conference; (Meeting Poster)  
 LA English  
 ED Entered STN: 16 Jul 2003  
 Last Updated on STN: 16 Jul 2003  
 AB Central cannabinoid systems are involved in regulation of energy  
 homeostasis. Cannabinoid CB1 receptor inverse agonists suppress appetite  
 and reduce body weight in various species. Exercise enhances fatty acid  
 oxidation and stimulates lipolysis. These studies tested the hypothesis  
 that voluntary running wheel exercise would potentiate the effects of  
 AM251, a CB1 receptor inverse agonist, on food intake and body weight loss  
 in murine models of obesity. ob/ob, A(y)/a (agouti yellow  
 obese), and C57BL/6J mice were treated orally with vehicle, 1, 3  
 or 10 mg/kg of AM251 one hour before lights off. The suppressive effects  
 of AM251 on overnight food intake (FI), body weight (BW), and water intake  
 (WI) were significant at 3 and 10 mg/kg in ob/ob mice. The high dose (10  
 mg/kg) of AM251 decreased FI and BW while it did not influence WI in  
 A(y)/a mice. Feeding frequency and duration were suppressed for 4-6 hours  
 following AM251 treatment in ob/ob and A(y)/a mice. AM251 at these doses  
 had no impact on the appetitive behavior or body weight of lean C57BL/6J  
 mice. After a 1-week wash-out period, mice were given running wheels in  
 their home cages and were treated with AM251. When coupled with running  
 wheel access, all animals had increased sensitivity to AM251. AM251 at 1  
 mg/kg, which did not decrease FI or BW in non-exercising animals,  
 suppressed FI and BW gain in ob/ob mice. Obese A(y)/a and lean  
 C57BL/6J mice with running wheel access lost BW following AM251 (at all  
 doses). Food intake of C57BL/6J mice given running wheels was unchanged.  
 Voluntary exercise can potentiate the effects of AM251 on energy  
 homeostasis and body weight loss in lean and obese mice.  
 TI VOLUNTARY EXERCISE FACILITATES THE EFFECTS OF AM251 ON BODY WEIGHT LOSS IN  
 GENETICALLY OBESE AND WILDTYPE MICE.  
 AB. . . the effects of AM251, a CB1 receptor inverse agonist, on food intake  
 and body weight loss in murine models of obesity. ob/ob, A(y)/a  
 (agouti yellow obese), and C57BL/6J mice were treated orally  
 with vehicle, 1, 3 or 10 mg/kg of AM251 one hour before lights off. . .  
 1 mg/kg, which did not decrease FI or BW in non-exercising animals,  
 suppressed FI and BW gain in ob/ob mice. Obese A(y)/a and lean  
 C57BL/6J mice with running wheel access lost BW following AM251 (at all  
 doses). Food intake of C57BL/6J. . . was unchanged. Voluntary  
 exercise can potentiate the effects of AM251 on energy homeostasis and  
 body weight loss in lean and obese mice.  
 IT Major Concepts  
 Behavior; Metabolism; Nutrition  
 IT Diseases  
 obesity: nutritional disease  
 Obesity (MeSH)  
 IT Chemicals & Biochemicals  
 AM251: CB1 receptor agonist  
 RN 51709-03-6Q (AM251)  
 183232-66-8Q (AM251)  
 L9 ANSWER 3 OF 14 BIOSIS COPYRIGHT (c) 2006 The Thomson Corporation on STN

AN 2002:529351 BIOSIS  
DN PREV200200529351  
TI Effect of a 28-d treatment with L-796568, a novel beta3-adrenergic  
receptor agonist, on energy expenditure and body composition in  
obese men.  
AU Larsen, Thomas M. [Reprint author]; Toubro, Soren; van Baak, Marleen A.;  
Gottesdiener, Keith M.; Larson, Patrick; Saris, Wim H. M.; Astrup, Arne  
CS Research Department of Human Nutrition, Royal Veterinary and Agricultural  
University, Rolighedsvej 30, 1958, Frederiksberg, Copenhagen, Denmark  
tml@kvl.dk  
SO American Journal of Clinical Nutrition, (October, 2002) Vol. 76, No. 4,  
pp. 780-788. print.  
CODEN: AJCNAC. ISSN: 0002-9165.  
DT Article  
LA English  
ED Entered STN: 16 Oct 2002  
Last Updated on STN: 5 Dec 2002  
AB Background: Stimulation of energy expenditure (EE) with selective  
thermogenic beta-adrenergic agonists may be a promising approach for  
treating obesity. Objective: We analyzed the effects of the  
highly selective human beta3-adrenergic agonist L-796568 on 24-h EE,  
substrate oxidation, and body composition in obese,  
weight-stable men. Design: In this 2-center, double-blind, randomized,  
parallel-group study, we measured 24-h EE before and after 28 d of  
treatment with L-796568 (375 mg/d) or placebo during weight maintenance  
(ie, without dietary intervention) in nondiabetic, nonsmoking men aged  
25-49 y with body mass index (in kg/m2) of 28-35 (n=10 subjects per  
treatment group). Results: The mean change in 24-h EE from before to  
after treatment did not differ significantly between groups (92+-586 and  
86+-512 kJ/24 h for the L-796568 and placebo groups, respectively). The  
change in 24-h nonprotein respiratory quotient from before to after  
treatment did not differ significantly between groups (0.009+-0.021 and  
0.009+-0.029, respectively). No changes in glucose tolerance were  
observed, but triacylglycerol concentrations decreased significantly with  
L-796568 treatment compared with placebo (-0.76+-0.76 and 0.42+-0.31  
mmol/L, respectively; P<0.002). Overall, treatment-related changes in  
body composition were not observed, but higher plasma L-796568  
concentrations in the L-796568 group were associated with greater  
decreases in fat mass (r=-0.69, P<0.03). Conclusions: Treatment with  
L-796568 for 28 d had no major lipolytic or thermogenic effect but it  
lowered triacylglycerol concentrations. This lack of chronic effect on  
energy balance is likely explained by insufficient recruitment of  
beta3-responsive tissues in humans, down-regulation of the  
beta3-adrenergic receptor-mediated effects with chronic dosing, or both.  
TI Effect of a 28-d treatment with L-796568, a novel beta3-adrenergic  
receptor agonist, on energy expenditure and body composition in  
obese men.  
AB Background: Stimulation of energy expenditure (EE) with selective  
thermogenic beta-adrenergic agonists may be a promising approach for  
treating obesity. Objective: We analyzed the effects of the  
highly selective human beta3-adrenergic agonist L-796568 on 24-h EE,  
substrate oxidation, and body composition in obese,  
weight-stable men. Design: In this 2-center, double-blind, randomized,  
parallel-group study, we measured 24-h EE before and after 28 d of.  
IT Major Concepts  
Neurology (Human Medicine, Medical Sciences); Nutrition; Pharmacology  
IT Diseases  
obesity: nutritional disease, diet therapy, drug therapy  
Obesity (MeSH)  
IT Chemicals & Biochemicals  
L-796568: adrenergic antagonist-drug, anorexic-drug, autonomic-drug,  
beta-adrenergic antagonist-drug, 28-day treatment, beta-3-adrenergic  
receptor agonist, thermogenic; beta-3-adrenergic receptor; . . .  
RN 211031-81-1 (L-796568)

L9 ANSWER 4 OF 14 CAPLUS COPYRIGHT 2006 ACS on STN

AN 2002:763926 CAPLUS

DN 137:288901

TI Effect of a 28-d treatment with L-796568, a novel  $\beta$ 3-adrenergic receptor agonist, on energy expenditure and body composition in obese men

AU Larsen, Thomas M.; Toubro, Soren; van Baak, Marleen A.; Gottesdiener, Keith M.; Larson, Patrick; Saris, Wim H. M.; Astrup, Arne

CS Research Department of Human Nutrition, The Royal Veterinary and Agricultural University, Copenhagen, Den.

SO American Journal of Clinical Nutrition (2002), 76(4), 780-788  
CODEN: AJCNAC; ISSN: 0002-9165

PB American Society for Clinical Nutrition

DT Journal

LA English

AB Stimulation of energy expenditure (EE) with selective thermogenic  $\beta$ -adrenergic agonists may be a promising approach for treating obesity. We analyzed the effects of the highly selective human  $\beta$ 3-adrenergic agonist L-796568 on 24-h EE, substrate oxidation, and body composition in obese, weight-stable men. In this 2-center, double-blind, randomized, parallel-group study, we measured 24-h EE before and after 28 d of treatment with L-796568 (375 mg/d) or placebo during weight maintenance (ie, without dietary intervention) in nondiabetic, nonsmoking men aged 25-49 yr with body mass index (in kg/m<sup>2</sup>) of 28-35 (n = 10 subjects per treatment group). The mean change in 24-h EE from before to after treatment did not differ significantly between groups (92 $\pm$ 586 and 86 $\pm$ 512 kJ/24 h for the L-796568 and placebo groups, resp.). The change in 24-h nonprotein RQ from before to after treatment did not differ significantly between groups (0.009 $\pm$ 0.021 and 0.009 $\pm$ 0.029, resp.). No changes in glucose tolerance were observed, but triacylglycerol concns. decreased significantly with L-796568 treatment compared with placebo (-0.76 $\pm$ 0.76 and 0.42 $\pm$ 0.31 mmol/L, resp.; P < 0.002). Overall, treatment-related changes in body composition were not observed, but higher plasma

L-796568 concns. in the L-796568 group were associated with greater decreases in fat mass (r = -0.69, P < 0.03). Treatment with L-796568 for 28 d had no major lipolytic or thermogenic effect but it lowered triacylglycerol concns. This lack of chronic effect on energy balance is likely explained by insufficient recruitment of  $\beta$ 3-responsive tissues in humans, down-regulation of the  $\beta$ 3-adrenergic receptor-mediated effects with chronic dosing, or both.

RE.CNT 45 THERE ARE 45 CITED REFERENCES AVAILABLE FOR THIS RECORD  
ALL CITATIONS AVAILABLE IN THE RE FORMAT

TI Effect of a 28-d treatment with L-796568, a novel  $\beta$ 3-adrenergic receptor agonist, on energy expenditure and body composition in obese men

AB Stimulation of energy expenditure (EE) with selective thermogenic  $\beta$ -adrenergic agonists may be a promising approach for treating obesity. We analyzed the effects of the highly selective human  $\beta$ 3-adrenergic agonist L-796568 on 24-h EE, substrate oxidation, and body composition in obese, weight-stable men. In this 2-center, double-blind, randomized, parallel-group study, we measured 24-h EE before and after 28 d of treatment with L-796568 (375 mg/d) or placebo during weight maintenance (ie, without dietary intervention) in nondiabetic, nonsmoking men aged 25-49 yr with body mass index (in kg/m<sup>2</sup>) of 28-35 (n = 10 subjects per treatment group). The mean change in 24-h EE from before to after treatment did not differ significantly between groups (92 $\pm$ 586 and 86 $\pm$ 512 kJ/24 h for the L-796568 and placebo groups, resp.). The change in 24-h nonprotein RQ from before to after treatment did not differ significantly between groups (0.009 $\pm$ 0.021 and 0.009 $\pm$ 0.029, resp.). No changes in glucose tolerance were observed, but triacylglycerol concns. decreased significantly with L-796568 treatment compared with placebo (-0.76 $\pm$ 0.76 and 0.42 $\pm$ 0.31 mmol/L, resp.; P < 0.002). Overall,

*dupl*

treatment-related changes in body composition were not observed, but higher plasma

L-796568 concns. in the L-796568 group were associated with greater decreases in fat mass ( $r = -0.69$ ,  $P < 0.03$ ). Treatment with L-796568 for 28 d had no major lipolytic or thermogenic effect but it lowered triacylglycerol concns. This lack of chronic effect on energy balance is likely explained by insufficient recruitment of  $\beta_3$ -responsive tissues in humans, down-regulation of the  $\beta_3$ -adrenergic receptor-mediated effects with chronic dosing, or both.

ST L796568 beta3 adrenergic receptor energy expenditure obese thermogenesis

IT Antiobesity agents  
Energy metabolism, animal  
Human

Obesity

Thermogenesis, biological

(effect of a 28-d treatment with L-796568, a novel  $\beta_3$ -adrenergic receptor agonist, on energy expenditure and body composition in obese men)

IT Fatty acids, biological studies

Glycerides, biological studies

Lipolysis

RL: BSU (Biological study, unclassified); BIOL (Biological study)

(effect of a 28-d treatment with L-796568, a novel  $\beta_3$ -adrenergic receptor agonist, on energy expenditure and body composition in obese men)

IT Body weight

(lean; effect of a 28-d treatment with L-796568, a novel  $\beta_3$ -adrenergic receptor agonist, on energy expenditure and body composition in obese men)

IT Adrenoceptor agonists

( $\beta_3$ -; effect of a 28-d treatment with L-796568, a novel  $\beta_3$ -adrenergic receptor agonist, on energy expenditure and body composition in obese men)

IT 56-81-5, Glycerol, biological studies 57-88-5, Cholesterol, biological studies

RL: BSU (Biological study, unclassified); BIOL (Biological study)

(effect of a 28-d treatment with L-796568, a novel  $\beta_3$ -adrenergic receptor agonist, on energy expenditure and body composition in obese men)

IT 211031-81-1, L-796568

RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(effect of a 28-d treatment with L-796568, a novel  $\beta_3$ -adrenergic receptor agonist, on energy expenditure and body composition in obese men)

L9 ANSWER 5 OF 14 CAPLUS COPYRIGHT 2006 ACS on STN

AN 2002:363839 CAPLUS

DN 137:15695

TI Acute effect of L-796568, a novel  $\beta_3$ -adrenergic receptor agonist, on energy expenditure in obese men

AU Van Baak, Marleen A.; Hul, Gabby B. J.; Toubro, Soren; Astrup, Arne; Gottesdiener, Keith M.; DeSmet, Marina; Saris, Wim H. M.

CS Nutrition and Toxicology Research Institute (NUTRIM), Maastricht University, Maastricht, 6200 MD, Neth.

SO Clinical Pharmacology & Therapeutics (St. Louis, MO, United States) (2002), 71(4), 272-279

CODEN: CLPTAT; ISSN: 0009-9236

PB Mosby, Inc.

DT Journal

LA English

AB Our objective was to investigate the thermogenic efficacy of single oral doses of the novel  $\beta_3$ -adrenergic receptor agonist L-796568

[(R)-N-[4-[2-[[2-hydroxy-2-(3-pyridinyl) ethyl]amino]ethyl]-phenyl]-4-[4-[4-(trifluoromethyl)phenyl] thiazol-2-yl]-benzenesulfonamide, dihydrochloride] in humans. Twelve healthy overweight to obese men participated in this 2-center, 3-period, randomized, placebo-controlled, crossover trial. In each period subjects received 250 mg L-796568, 1000 mg L-796568, or placebo. Energy expenditure and RQ were determined by indirect calorimetry; blood samples were taken; and ear

temperature,

heart rate, and blood pressure were measured at baseline and during the 4-h period after administration. Energy expenditure increased significantly after the 1000-mg dose (about 8%) and this was accompanied by an increase in plasma glycerol and free fatty acid concns. Systolic blood pressure also increased significantly. No changes in heart rate, diastolic blood pressure, ear temperature, plasma catecholamine, potassium, or leptin were found. Single-dose administration of 1000 mg of the novel  $\beta_3$ -adrenergic receptor agonist L-796568 increased lipolysis and energy expenditure in overweight men. This is the first study to show such an effect of  $\beta_3$ -adrenergic receptor agonists in humans without significant evidence for  $\beta_2$ -adrenergic receptor involvement.

RE.CNT 34 THERE ARE 34 CITED REFERENCES AVAILABLE FOR THIS RECORD

ALL CITATIONS AVAILABLE IN THE RE FORMAT

TI Acute effect of L-796568, a novel  $\beta_3$ -adrenergic receptor agonist, on energy expenditure in obese men

AB Our objective was to investigate the thermogenic efficacy of single oral doses of the novel  $\beta_3$ -adrenergic receptor agonist L-796568 [(R)-N-[4-[2-[[2-hydroxy-2-(3-pyridinyl) ethyl]amino]ethyl]-phenyl]-4-[4-[4-(trifluoromethyl)phenyl] thiazol-2-yl]-benzenesulfonamide, dihydrochloride] in humans. Twelve healthy overweight to obese men participated in this 2-center, 3-period, randomized, placebo-controlled, crossover trial. In each period subjects received 250 mg L-796568, 1000 mg L-796568, or placebo. Energy expenditure and RQ were determined by indirect calorimetry; blood samples were taken; and ear

temperature,

heart rate, and blood pressure were measured at baseline and during the 4-h period after administration. Energy expenditure increased significantly after the 1000-mg dose (about 8%) and this was accompanied by an increase in plasma glycerol and free fatty acid concns. Systolic blood pressure also increased significantly. No changes in heart rate, diastolic blood pressure, ear temperature, plasma catecholamine, potassium, or leptin were found. Single-dose administration of 1000 mg of the novel  $\beta_3$ -adrenergic receptor agonist L-796568 increased lipolysis and energy expenditure in overweight men. This is the first study to show such an effect of  $\beta_3$ -adrenergic receptor agonists in humans without significant evidence for  $\beta_2$ -adrenergic receptor involvement.

ST L796568 adrenoceptor agonist antiobesity energy expenditure lipolysis thermogenesis obesity

IT Antiobesity agents

Cardiovascular system

Energy metabolism, animal

Human

Thermogenesis, biological

(effect of L-796568, a novel  $\beta_3$ -adrenergic receptor agonist, on energy expenditure in obese men)

IT Fatty acids, biological studies

Lipolysis

RL: BSU (Biological study, unclassified); BIOL (Biological study)

(effect of L-796568, a novel  $\beta_3$ -adrenergic receptor agonist, on energy expenditure in obese men)

IT Adrenoceptor agonists

( $\beta_3$ -; effect of L-796568, a novel  $\beta_3$ -adrenergic receptor agonist, on energy expenditure in obese men)

IT 211031-81-1, L 796568

RL: ADV (Adverse effect, including toxicity); DMA (Drug mechanism of action); PAC (Pharmacological activity); THU (Therapeutic use); BIOL

(Biological study); USES (Uses)

(effect of L-796568, a novel  $\beta$ 3-adrenergic receptor agonist, on energy expenditure in obese men)

IT 56-81-5, Glycerol, biological studies

RL: BSU (Biological study, unclassified); BIOL (Biological study)  
(effect of L-796568, a novel  $\beta$ 3-adrenergic receptor agonist, on energy expenditure in obese men)

L9 ANSWER 6 OF 14 CAPLUS COPYRIGHT 2006 ACS on STN

AN 1998:527330 CAPLUS

DN 129:161557

TI Thiazole benzenesulfonamides as  $\beta$ 3 agonists for the treatment of diabetes and obesity

IN Mathvink, Robert J.; Parmee, Emma R.; Tolman, Samuel; Weber, Ann E.

PA Merck & Co., Inc., USA

SO PCT Int. Appl., 64 pp.

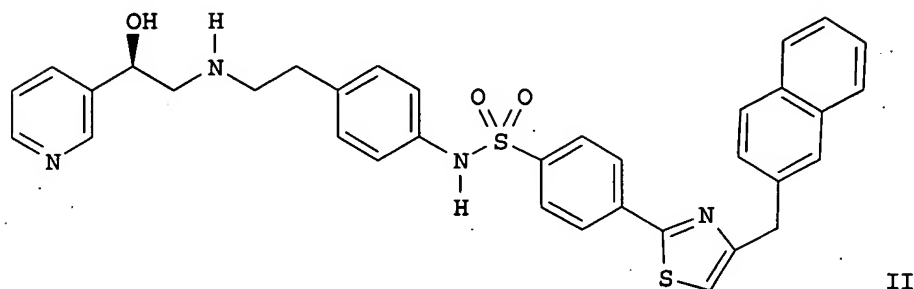
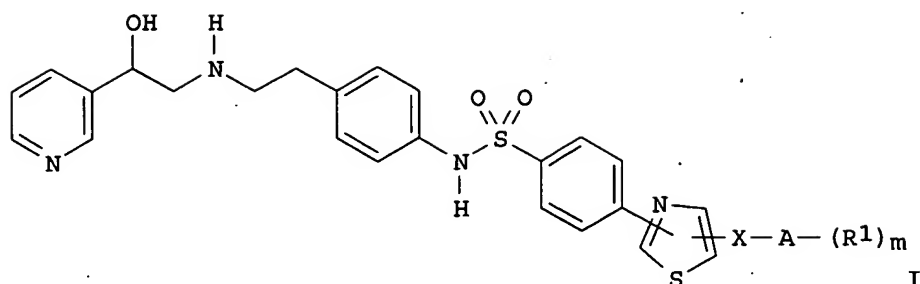
CODEN: PIXXD2

DT Patent

LA English

FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 9832753	A1	19980730	WO 1998-US1317	19980123
	W: AL, AM, AU, AZ, BA, BB, BG, BR, BY, CA, CN, CU, CZ, EE, GE, GW, HU, ID, IL, IS, JP, KG, KR, KZ, LC, LK, LR, LT, LV, MD, MG, MK, MN, MX, NO, NZ, PL, RO, RU, SG, SI, SK, SL, TJ, TM, TR, TT, UA, US, UZ, VN, YU				
	RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
	US 6011048	A	20000104	US 1998-7363	19980115
	CA 2278739	AA	19980730	CA 1998-2278739	19980123
	AU 9860384	A1	19980818	AU 1998-60384	19980123
	AU 728812	B2	20010118		
	EP 968209	A1	20000105	EP 1998-903677	19980123
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, PT, IE, SI, LT, LV, FI, RO				
	EE 9900328	A	20000215	EE 1999-328	19980123
	BR 9807096	A	20000418	BR 1998-7096	19980123
	TR 9902442	T2	20000721	TR 1999-2442	19980123
	JP 2001509166	T2	20010710	JP 1998-532148	19980123
	ZA 9800647	A	19980728	ZA 1998-647	19980127
	NO 9903646	A	19990927	NO 1999-3646	19990727
PRAI	US 1997-36760P	P	19970128		
	GB 1997-5041	A	19970312		
	WO 1998-US1317	W	19980123		
OS	MARPAT 129:161557				
GI					



AB Thiazole-substituted benzenesulfonamides I [X = bond, C1-3 alkylene with optional Me or halo substituents or a contained O atom; m = 0-5; A = benzene, heterocycle, benzo-fused carbocycle, or hetero-fused carbo- or heterocycle; R1 = (un)substituted alkyl, cycloalkyl, oxo, halo, cyano, (un)substituted amino, CO2H or esters, etc.] and their prodrugs and pharmaceutically acceptable salts are disclosed. The compds. are  $\beta_3$  adrenergic receptor agonists (no data) with very little  $\beta_1$  and  $\beta_2$  adrenergic receptor activity, and as such are capable of increasing lipolysis and cellular energy expenditure. The compds. thus have potent activity in the treatment of Type II diabetes and obesity. The compds. can also be used to lower triglyceride levels and cholesterol levels or raise high d. lipoprotein levels, or to decrease gut motility. In addition, the compds. can be used to reduce neurogenic inflammation, or as antidepressants. Compns. and methods of use are also disclosed. The compds. are prepared, e.g., by coupling an aminoalkylphenyl-sulfonamide with an appropriately substituted epoxide. Alternatively, for instance, 2-naphthylmethyl chloromethyl ketone was cyclized with 4-bromothiobenzamide to give 2-(4-bromophenyl)-4-(2-naphthylmethyl)thiazole. The latter bromide was lithiated and then treated with SO<sub>2</sub> followed by NCS to give the corresponding sulfonyl chloride. Amidation of this with the corresponding enantiomeric amine gave title compound II.

RE.CNT 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD  
ALL CITATIONS AVAILABLE IN THE RE FORMAT

TI Thiazole benzenesulfonamides as  $\beta_3$  agonists for the treatment of diabetes and obesity

AB Thiazole-substituted benzenesulfonamides I [X = bond, C1-3 alkylene with optional Me or halo substituents or a contained O atom; m = 0-5; A = benzene, heterocycle, benzo-fused carbocycle, or hetero-fused carbo- or heterocycle; R1 = (un)substituted alkyl, cycloalkyl, oxo, halo, cyano, (un)substituted amino, CO2H or esters, etc.] and their prodrugs and pharmaceutically acceptable salts are disclosed. The compds. are  $\beta_3$  adrenergic receptor agonists (no data) with very little  $\beta_1$  and  $\beta_2$  adrenergic receptor activity, and as such are capable of increasing lipolysis and cellular energy expenditure. The compds. thus have potent activity in the treatment of Type II diabetes and obesity. The compds. can also be used to lower triglyceride levels and cholesterol levels or raise high d. lipoprotein levels, or to decrease gut motility. In addition, the compds. can be used to reduce



neurogenic inflammation, or as antidepressants. Compns. and methods of use are also disclosed. The compds. are prepared, e.g., by coupling an aminoalkylphenyl-sulfonamide with an appropriately substituted epoxide. Alternatively, for instance, 2-naphthylmethyl chloromethyl ketone was cyclized with 4-bromothiobenzamide to give 2-(4-bromophenyl)-4-(2-naphthylmethyl)thiazole. The latter bromide was lithiated and then treated with SO<sub>2</sub> followed by NCS to give the corresponding sulfonyl chloride. Amidation of this with the corresponding enantiomeric amine gave title compound II.

IT	211030-99-8P	211031-01-5P	211031-03-7P	211031-05-9P	211031-07-1P
	211031-09-3P	211031-11-7P	211031-13-9P	211031-15-1P	211031-17-3P
	211031-19-5P	211031-21-9P	211031-23-1P	211031-25-3P	211031-27-5P
	211031-29-7P	211031-31-1P	211031-33-3P	211031-35-5P	211031-37-7P
	211031-39-9P	211031-41-3P	211031-43-5P	211031-45-7P	211031-47-9P
	211031-49-1P	211031-51-5P	211031-53-7P	211031-55-9P	211031-57-1P
	211031-59-3P	211031-61-7P	211031-63-9P	211031-65-1P	211031-67-3P
	211031-69-5P	211031-71-9P	211031-73-1P	211031-75-3P	211031-77-5P
	211031-79-7P	211031-81-1P	211031-83-3P	211031-85-5P	
	211032-15-4P	211032-17-6P	211032-19-8P	211032-21-2P	211032-23-4P
	211032-25-6P	211032-27-8P	211032-29-0P	211032-31-4P	211032-33-6P
	211032-35-8P	211032-37-0P	211032-39-2P	211032-41-6P	211032-43-8P
	211032-45-0P	211032-47-2P	211032-49-4P	211032-51-8P	211032-53-0P
	211032-55-2P	211032-57-4P	211032-59-6P	211032-61-0P	211032-64-3P
	211032-67-6P	211032-70-1P	211032-73-4P	211032-75-6P	211032-78-9P
	211032-81-4P	211032-84-7P	211032-87-0P	211032-89-2P	211032-91-6P
	211032-93-8P	211032-95-0P	211032-97-2P	211033-00-0P	211033-03-3P
	211033-05-5P				

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)  
(preparation of thiazole benzenesulfonamides as  $\beta_3$  agonists)

L9 ANSWER 7 OF 14 Elsevier BIOBASE COPYRIGHT 2006 Elsevier Science B.V. on STN  
AN 2002219708 ESBIODBASE  
TI Effect of a 28-d treatment with L-796568, a novel  $\beta$ .sub.3-adrenergic receptor agonist, on energy expenditure and body composition in obese men  
AU Larsen T.M.; Toubro S.; Van Baak M.A.; Gottesdiener K.M.; Larson P.; Saris W.H.M.; Astrup A.  
CS T.M. Larsen, Res. Department of Human Nutrition, Roy. Vet./Agricultural University, Rolighedsvej 30, 1958 Frederiksberg, Copenhagen, Denmark. E-mail: tml@kvl.dk  
SO American Journal of Clinical Nutrition, (2002), 76/4 (780-788), 45 reference(s)  
CODEN: AJCNAC ISSN: 0002-9165  
DT Journal; Article  
CY United States  
LA English  
SL English  
AB Background: Stimulation of energy expenditure (EE) with selective thermogenic  $\beta$ -adrenergic agonists may be a promising approach for treating obesity. Objective: We analyzed the effects of the highly selective human  $\beta$ -adrenergic agonist L-796568 on 24-h EE, substrate oxidation, and body composition in obese, weight-stable men. Design: In this 2-center, double-blind, randomized, parallel-group study, we measured 24-h EE before and after 28 d of treatment with L-796568 (375 mg/d) or placebo during weight maintenance (ie, without dietary intervention) in nondiabetic, nonsmoking men aged 25-49 y with body mass index (in kg/m.sup.2) of 28-35 (n = 10 subjects per treatment group). Results: The mean change in 24-h EE from before to after treatment did not differ significantly between groups ( $92 \pm 586$  and  $86 \pm 512$  kJ/24 h for the L-796568 and placebo groups, respectively). The change

*dupl.*

in 24-h nonprotein respiratory quotient from before to after treatment did not differ significantly between groups ( $0.009 \pm 0.021$  and  $0.009 \pm 0.029$ , respectively). No changes in glucose tolerance were observed, but triacylglycerol concentrations decreased significantly with L-796568 treatment compared with placebo ( $-0.76 \pm 0.76$  and  $0.42 \pm 0.31$  mmol/L, respectively;  $P < 0.002$ ). Overall, treatment-related changes in body composition were not observed, but higher plasma L-796568 concentrations in the L-796568 group were associated with greater decreases in fat mass ( $r = -0.69$ ,  $P < 0.03$ ). Conclusions: Treatment with L-796568 for 28 d had no major lipolytic or thermogenic effect but it lowered triacylglycerol concentrations. This lack of chronic effect on energy balance is likely explained by insufficient recruitment of  $\beta$ .sub.3-responsive tissues in humans, down-regulation of the  $\beta$ .sub.3-adrenergic receptor-mediated effects with chronic dosing, or both.

- TI Effect of a 28-d treatment with L-796568, a novel  $\beta$ .sub.3-adrenergic receptor agonist, on energy expenditure and body composition in obese men
- AB Background: Stimulation of energy expenditure (EE) with selective thermogenic  $\beta$ -adrenergic agonists may be a promising approach for treating obesity. Objective: We analyzed the effects of the highly selective human  $\beta$ -adrenergic agonist L-796568 on 24-h EE, substrate oxidation, and body composition in obese, weight-stable men. Design: In this 2-center, double-blind, randomized, parallel-group study, we measured 24-h EE before and after 28 d of treatment with L-796568 (375 mg/d) or placebo during weight maintenance (ie, without dietary intervention) in nondiabetic, nonsmoking men aged 25-49 y with body. . . to after treatment did not differ significantly between groups ( $92 \pm 586$  and  $86 \pm 512$  kJ/24 h for the L-796568 and placebo groups, respectively). The change in 24-h nonprotein respiratory quotient from before to after treatment did not differ significantly. . .  $\pm 0.021$  and  $0.009 \pm 0.029$ , respectively). No changes in glucose tolerance were observed, but triacylglycerol concentrations decreased significantly with L-796568 treatment compared with placebo ( $-0.76 \pm 0.76$  and  $0.42 \pm 0.31$  mmol/L, respectively;  $P < 0.002$ ). Overall, treatment-related changes in body composition were not observed, but higher plasma L-796568 concentrations in the L-796568 group were associated with greater decreases in fat mass ( $r = -0.69$ ,  $P < 0.03$ ). Conclusions: Treatment with L-796568 for 28 d had no major lipolytic or thermogenic effect but it lowered triacylglycerol concentrations. This lack of chronic effect.
- ST L-796568;  $\beta$ .sub.3-adrenergic receptor;  $\beta$ .sub.3-adrenergic receptor agonist;  $\beta$ .sub.3 agonist; Selectivity; Energy expenditure; Lipolysis; Respiratory quotient; Indirect calorimetry; Triacylglycerol; Obesity; Obese men
- L9 ANSWER 8 OF 14 PASCAL COPYRIGHT 2006 INIST-CNRS. ALL RIGHTS RESERVED. on STN
- AN 2002-0579884 PASCAL
- CP Copyright .COPYRG. 2002 INIST-CNRS. All rights reserved.
- TIEN Effect of a 28-d treatment with L-796568, a novel  $\beta$ .sub.3-adrenergic receptor agonist, on energy expenditure and body composition in obese men
- AU LARSEN Thomas M.; TOUBRO Soren; VAN BAAK Marleen A.; GOTTESDIENER Keith M.; LARSON Patrick; SARIS Wim H. M.; ASTROP Arne
- CS Research Department of Human Nutrition, The Royal Veterinary and Agricultural University, Copenhagen, Denmark; Nutrition and Toxicology Research Institute (NUTRIM), Department of Human Biology, Maastricht University, Maastricht, Netherlands; Merck & Co, Rahway, NJ, United States

SO The American journal of clinical nutrition, (2002), 76(4), 780-788, 45  
refs.  
ISSN: 0002-9165 CODEN: AJCNAC

DT Journal  
BL Analytic  
CY United States  
LA English  
AV INIST-8263, 354000109283810130  
CP Copyright .COPYRGT. 2002 INIST-CNRS. All rights reserved.  
AB Background: Stimulation of energy expenditure (EE) with selective thermogenic  $\beta$ -adrenergic agonists may be a promising approach for treating obesity. Objective: We analyzed the effects of the highly selective human  $\beta$ .sub.3-adrenergic agonist L-796568 on 24-h EE, substrate oxidation, and body composition in obese, weight-stable men. Design: In this 2-center, double-blind, randomized, parallel-group study, we measured 24-h EE before and after 28 d of treatment with L-796568 (375 mg/d) or placebo during weight maintenance (ie, without dietary intervention) in nondiabetic, nonsmoking men aged 25-49 y with body mass index (in kg/m.sup.2) of 28-35 (n = 10 subjects per treatment group). Results: The mean change in 24-h EE from before to after treatment did not differ significantly between groups ( $92 \pm 586$  and  $86 \pm 512$  kJ/24 h for the L-796568 and placebo groups, respectively). The change in 24-h nonprotein respiratory quotient from before to after treatment did not differ significantly between groups ( $0.009 \pm 0.021$  and  $0.009 \pm 0.029$ , respectively). No changes in glucose tolerance were observed, but triacylglycerol concentrations decreased significantly with L-796568 treatment compared with placebo ( $-0.76 \pm 0.76$  and  $0.42 \pm 0.31$  mmol/L, respectively;  $P < 0.002$ ). Overall, treatment-related changes in body composition were not observed, but higher plasma L-796568 concentrations in the L-796568 group were associated with greater decreases in fat mass ( $r = -0.69$ ,  $P < 0.03$ ). Conclusions: Treatment with L-796568 for 28 d had no major lipolytic or thermogenic effect but it lowered triacylglycerol concentrations. This lack of chronic effect on energy balance is likely explained by insufficient recruitment of  $\beta$ .sub.3-responsive tissues in humans, down-regulation of the  $\beta$ .sub.3-adrenergic receptormediated effects with chronic dosing, or both.

TIEN Effect of a 28-d treatment with L-796568, a novel  $\beta$ .sub.3-adrenergic receptor agonist, on energy expenditure and body composition in obese men

AB Background: Stimulation of energy expenditure (EE) with selective thermogenic  $\beta$ -adrenergic agonists may be a promising approach for treating obesity. Objective: We analyzed the effects of the highly selective human  $\beta$ .sub.3-adrenergic agonist L-796568 on 24-h EE, substrate oxidation, and body composition in obese, weight-stable men. Design: In this 2-center, double-blind, randomized, parallel-group study, we measured 24-h EE before and after 28 d of treatment with L-796568 (375 mg/d) or placebo during weight maintenance (ie, without dietary intervention) in nondiabetic, nonsmoking men aged 25-49 y with body. . . to after treatment did not differ significantly between groups ( $92 \pm 586$  and  $86 \pm 512$  kJ/24 h for the L-796568 and placebo groups, respectively). The change in 24-h nonprotein respiratory quotient from before to after treatment did not differ significantly. . .  $\pm 0.021$  and  $0.009 \pm 0.029$ , respectively). No changes in glucose tolerance were observed, but triacylglycerol concentrations decreased significantly with L-796568 treatment compared with placebo ( $-0.76 \pm 0.76$  and  $0.42 \pm 0.31$  mmol/L, respectively;  $P < 0.002$ ). Overall, treatment-related changes in body composition were not observed, but higher plasma L-796568 concentrations in the L-796568 group were associated with greater decreases in fat mass ( $r = -0.69$ ,  $P < 0.03$ ). Conclusions: Treatment with L

Dupl

-796568 for 28 d had no major lipolytic or thermogenic effect but it lowered triacylglycerol concentrations. This lack of chronic effect.

CT Agonist;  $\beta$ 3-Adrenergic receptor; Treatment; Energetic cost; Body composition; Anthropometry; Indirect calorimetry; Obesity; Nutritional status; Respiratory quotient; Randomized design; Double blind study; Human; Male

L9 ANSWER 9 OF 14 PASCAL COPYRIGHT 2006 INIST-CNRS. ALL RIGHTS RESERVED.  
on STN

AN 2002-0455153 PASCAL

CP Copyright .COPYRGT. 2002 INIST-CNRS. All rights reserved.

TIEN Acute effect of L-796568, a novel  
 $\beta$ .sub.3-adrenergic receptor agonist, on energy expenditure in obese men

AU VAN BAAK Marleen A.; HUL Gabby B. J.; TOUBRO Siren; ASTRUP Arne; GOTTESDIENER Keith M.; DESMET Marina; SARIS Wim H. M.

CS Nutrition and Toxicology Research Institute (NUTRIM), Department of Human Biology, Maastricht University, Netherlands; Research Department of Human Nutrition, Royal Veterinary and Agricultural University, Copenhagen, Denmark; Merck & Co. Inc., Rahway, NJ, United States

SO Clinical pharmacology and therapeutics, (2002), 71(4), 272-279, 34 refs.  
ISSN: 0009-9236 CODEN: CLPTAT

DT Journal

BL Analytic

CY United States

LA English

AV INIST-1144, 354000108249030090

CP Copyright .COPYRGT. 2002 INIST-CNRS. All rights reserved.

AB Objective: Our objective was to investigate the thermogenic efficacy of single oral doses of the novel  $\beta$ .sub.3-adrenergic receptor agonist L-796568 [(R)-N-[4-[2-[[2-hydroxy-2-(3-pyridinyl)ethyl]amino]ethyl]-phenyl]-4-[4-(trifluoromethyl)phenyl]thiazol-2-yl]-benzenesulfonamide, dihydrochloride] in humans. Methods: Twelve healthy overweight to obese men participated in this 2-center, 3-period, randomized, placebo-controlled, crossover trial. In each period subjects received 250 mg L-796568, 1000 mg L-796568, or placebo. Energy expenditure and respiratory quotient were determined by indirect calorimetry; blood samples were taken; and ear temperature, heart rate, and blood pressure were measured at baseline and during the 4-hour period after administration. Results: Energy expenditure increased significantly after the 1000-mg dose (about 8%) and this was accompanied by an increase in plasma glycerol and free fatty acid concentrations. Systolic blood pressure also increased significantly. No changes in heart rate, diastolic blood pressure, ear temperature, plasma catecholamine, potassium, or leptin were found. Conclusions: Single-dose administration of 1000 mg of the novel  $\beta$ .sub.3-adrenergic receptor agonist L-796568 increased lipolysis and energy expenditure in overweight men. This is the first study to show such an effect of  $\beta$ .sub.3-adrenergic receptor agonists in humans without significant evidence for  $\beta$ .sub.2-adrenergic receptor involvement.

TIEN Acute effect of L-796568, a novel  
 $\beta$ .sub.3-adrenergic receptor agonist, on energy expenditure in obese men

AB Objective: Our objective was to investigate the thermogenic efficacy of single oral doses of the novel  $\beta$ .sub.3-adrenergic receptor agonist L-796568 [(R)-N-[4-[2-[[2-hydroxy-2-(3-pyridinyl)ethyl]amino]ethyl]-phenyl]-4-[4-(trifluoromethyl)phenyl]thiazol-2-yl]-benzenesulfonamide, dihydrochloride] in humans. Methods: Twelve healthy overweight to obese men participated in this 2-center, 3-period, randomized, placebo-controlled, crossover trial. In each period subjects received 250 mg L-796568, 1000 mg L-796568, or

*dupl*

placebo. Energy expenditure and respiratory quotient were determined by indirect calorimetry; blood samples were taken; and ear temperature, heart. . . temperature, plasma catecholamine, potassium, or leptin were found. Conclusions: Single-dose administration of 1000 mg of the novel  $\beta$ .sub.3-adrenergic receptor agonist L-796568 increased lipolysis and energy expenditure in overweight men. This is the first study to show such an effect of  $\beta$ .sub.3-adrenergic. . .

CT Obesity;  $\beta$ 3-Adrenergic receptor; Agonist; Energy; Expenditure; Biological activity; Single dose; Oral administration; Controlled therapeutic trial; Human; Hemodynamics; Body temperature; Lipolysis; Treatment; . . .  
CTFR. . . Energie; Depense; Activite biologique; Dose unique; Voie orale; Essai therapeutique controle; Homme; Hemodynamique; Temperature corporelle; Lipolyse; Traitement; Chimiotherapie; Etat nutritionnel; L 796568

L9 ANSWER 10 OF 14 SCISEARCH COPYRIGHT (c) 2006 The Thomson Corporation on STN

AN 2002:783618 SCISEARCH

GA The Genuine Article (R) Number: 595GV

TI Effect of a 28-d treatment with L-796568, a novel beta(3)-adrenergic receptor agonist, on energy expenditure and body composition in obese men

AU Larsen T M (Reprint); Toubro S; van Baak M A; Gottesdiener K M; Larson P; Saris W H M; Astrup A

CS Royal Vet & Agr Univ, Res Dept Human Nutr, Rolighedsvej 30, DK-1958 Frederiksberg, Denmark (Reprint); Royal Vet & Agr Univ, Res Dept Human Nutr, DK-1958 Frederiksberg, Denmark; Maastricht Univ, Nutr & Toxicol Res Inst NUTRIM, Dept Human Biol, Maastricht, Netherlands; Merck & Co Inc, Rahway, NJ 07065 USA

CYA Denmark; Netherlands; USA

SO AMERICAN JOURNAL OF CLINICAL NUTRITION, (OCT 2002) Vol. 76, No. 4, pp. 780-788.

ISSN: 0002-9165.

PB AMER SOC CLINICAL NUTRITION, 9650 ROCKVILLE PIKE, SUBSCRIPTIONS, RM L-3300, BETHESDA, MD 20814-3998 USA.

DT Article; Journal

LA English

REC Reference Count: 45

ED Entered STN: 18 Oct 2002

Last Updated on STN: 18 Oct 2002

\*ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS\*

AB Background: Stimulation of energy expenditure (EE) with selective thermogenic P-adrenergic agonists may be a promising approach for treating obesity.

Objective: We analyzed the effects of the highly selective human beta(3)-adrenergic agonist L-796568 on 24-h EE, substrate oxidation, and body composition in obese, weight-stable men.

Design: In this 2-center, double-blind, randomized, parallel-group study, we measured 24-h EE before and after 28 d of treatment with L-796568 (375 mg/d) or placebo during weight maintenance (ie, without dietary intervention) in nondiabetic, nonsmoking men aged 25-49 y with body mass index (in kg/m(2)) of 28-35 (n = 10 subjects per treatment group).

Results: The mean change in 24-h EE from before to after treatment did not differ significantly between groups (92 586 and 86 512 kJ/24 h for the L-796568 and placebo groups, respectively). The change in 24-h nonprotein respiratory quotient from before to after treatment did not differ significantly between groups (0.009 +/- 0.021 and 0.009 +/- 0.029, respectively). No changes in glucose tolerance were observed, but triacylglycerol concentrations decreased significantly with L-796568 treatment compared with placebo (-0.76 +/- 0.76 and 0.42 +/- 0.31 mmol/L, respectively; P < 0.002). Overall,

*dupl*

treatment-related changes in body composition were not observed, but higher plasma L-796568 concentrations in the L-796568 group were associated with greater decreases in fat mass ( $r = -0.69$ ,  $P < 0.03$ ).

Conclusions: Treatment with L-796568 for 28 d had no major lipolytic or thermogenic effect but it lowered triacylglycerol concentrations. This lack of chronic effect on energy balance is likely explained by insufficient recruitment of beta(3)-responsive tissues in humans, down-regulation of the beta(3)-adrenergic receptor-mediated effects with chronic dosing, or both.

TI Effect of a 28-d treatment with L-796568, a novel beta(3)-adrenergic receptor agonist, on energy expenditure and body composition in obese men

AB Background: Stimulation of energy expenditure (EE) with selective thermogenic P-adrenergic agonists may be a promising approach for treating obesity.

Objective: We analyzed the effects of the highly selective human beta(3)-adrenergic agonist L-796568 on 24-h EE, substrate oxidation, and body composition in obese, weight-stable men.

Design: In this 2-center, double-blind, randomized, parallel-group study, we measured 24-h EE before and after 28 d of treatment with L-796568 (375 mg/d) or placebo during weight maintenance (ie, without dietary intervention) in nondiabetic, nonsmoking men aged 25-49 y with body. . . from before to after treatment did not differ significantly between groups (92 586 and 86 512 kJ/24 h for the L-796568 and placebo groups, respectively). The change in 24-h nonprotein respiratory quotient from before to after treatment did not differ significantly. . . +/- 0.021 and 0.009 +/- 0.029, respectively). No changes in glucose tolerance were observed, but triacylglycerol concentrations decreased significantly with L-796568 treatment compared with placebo (-0.76 +/- 0.76 and 0.42 +/- 0.31 mmol/L, respectively;  $P < 0.002$ ). Overall, treatment-related changes in body composition were not observed, but higher plasma L-796568 concentrations in the L-796568 group were associated with greater decreases in fat mass ( $r = -0.69$ ,  $P < 0.03$ ).

Conclusions: Treatment with L-796568 for 28 d had no major lipolytic or thermogenic effect but it lowered triacylglycerol concentrations. This lack of chronic effect. . .

ST Author Keywords: L-796568; beta(3)-adrenergic receptor; beta(3)-adrenergic receptor agonist; beta(3) agonist; selectivity; energy expenditure; lipolysis; respiratory quotient; indirect calorimetry; triacylglycerol; obesity; obese men

L9 ANSWER 11 OF 14 SCISEARCH COPYRIGHT (c) 2006 The Thomson Corporation on STN

AN 2002:353227 SCISEARCH

GA The Genuine Article (R) Number: 543XN

TI Acute effect of L-796568, a novel beta(3)-adrenergic receptor agonist, on energy expenditure in obese men

AU van Baak M A (Reprint); Hul G B J; Toubro S; Astrup A; Gottesdiener K M; DeSmet M; Saris W H M

CS Maastricht Univ, Dept Human Biol, Nutr & Toxicol Res Inst, POB 616, NL-6200 MD Maastricht, Netherlands (Reprint); Maastricht Univ, Dept Human Biol, Nutr & Toxicol Res Inst, NL-6200 MD Maastricht, Netherlands; Royal Vet & Agr Univ, Res Dept Human Nutr, Copenhagen, Denmark; Merck & Co Inc, Rahway, NJ 07065 USA

CYA Netherlands; Denmark; USA

SO CLINICAL PHARMACOLOGY & THERAPEUTICS, (APR 2002) Vol. 71, No. 4, pp. 272-279.

ISSN: 0009-9236.

PB MOSBY, INC, 11830 WESTLINE INDUSTRIAL DR, ST LOUIS, MO 63146-3318 USA.

DT Article; Journal

LA English

REC Reference Count: 34  
ED Entered STN: 10 May 2002  
Last Updated on STN: 10 May 2002  
\*ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS\*

AB Objective: Our objective was to investigate the thermogenic efficacy of single oral doses of the novel beta(3)-adrenergic receptor agonist L-796568 [(R)-N-[4-[2-[[2-hydroxy-2-(3-pyridinyl)ethyl]amino]ethyl]phenyl]-4-[4-[4-(trifluoromethyl)phenyl]thiazol-2-yl]-benzenesulfonamide, dihydrochloride] in humans.

Methods: Twelve healthy overweight to obese men participated in this 2-center, 3-period, randomized, placebo-controlled, crossover trial. In each period subjects received 250 mg L-796568, 1000 mg L-796568, or placebo. Energy expenditure and respiratory quotient were determined by indirect calorimetry; blood samples were taken; and ear temperature, heart rate, and blood pressure were measured at baseline and during the 4-hour period after administration.

Results: Energy expenditure increased significantly after the 1000-mg dose (about 8%) and this was accompanied by an increase in plasma glycerol and free fatty acid concentrations. Systolic blood pressure also increased significantly. No changes in heart rate, diastolic blood pressure, ear temperature, plasma catecholamine, potassium, or leptin were found.

Conclusions: Single-dose administration of 1000 mg of the novel beta(3)-adrenergic receptor agonist L-796568 increased lipolysis and energy expenditure in overweight men. This is the first study to show such an effect of beta(3)-adrenergic receptor agonists in humans without significant evidence for beta(2)-adrenergic receptor involvement.

TI Acute effect of L-796568, a novel beta(3)-adrenergic receptor agonist, on energy expenditure in obese men

AB Objective: Our objective was to investigate the thermogenic efficacy of single oral doses of the novel beta(3)-adrenergic receptor agonist L-796568 [(R)-N-[4-[2-[[2-hydroxy-2-(3-pyridinyl)ethyl]amino]ethyl]phenyl]-4-[4-[4-(trifluoromethyl)phenyl]thiazol-2-yl]-benzenesulfonamide, dihydrochloride] in humans.

Methods: Twelve healthy overweight to obese men participated in this 2-center, 3-period, randomized, placebo-controlled, crossover trial. In each period subjects received 250 mg L-796568, 1000 mg L-796568, or placebo. Energy expenditure and respiratory quotient were determined by indirect calorimetry; blood samples were taken; and ear temperature, heart rate, temperature, plasma catecholamine, potassium, or leptin were found.

Conclusions: Single-dose administration of 1000 mg of the novel beta(3)-adrenergic receptor agonist L-796568 increased lipolysis and energy expenditure in overweight men. This is the first study to show such an effect of beta(3)-adrenergic.

L9 ANSWER 12 OF 14 SCISEARCH COPYRIGHT (c) 2006 The Thomson Corporation on STN

AN 2000:859460 SCISEARCH

GA The Genuine Article (R) Number: 364DE

TI Acute thermogenic effect of L-796568, a novel beta(3)-adrenoceptor agonist, in obese men

AU van Baak M A (Reprint); Hul G; Toubro S; Astrup A; Gottesdiener K M; DeSmer M; Saris W H M

CS Maastricht Univ, Maastricht, Netherlands; Royal Vet & Agr Univ, Copenhagen, Denmark; Merck & Co Inc, Rahway, NJ 07065 USA

CYA Netherlands; Denmark; USA

SO OBESITY RESEARCH, (OCT 2000) Vol. 8, Supp. [1], pp. 91S-91S. MA PB95. ISSN: 1071-7323.

PB NORTH AMER ASSOC STUDY OBESITY, 8630 FENTON ST, SUITE 918, SILVER SPRING, MD 20910 USA.

DT Conference; Journal

LA English  
REC Reference Count: 0  
ED Entered STN: 2000  
Last Updated on STN: 2000  
TI Acute thermogenic effect of L-796568, a novel  
beta(3)-adrenoceptor agonist, in obese men

L9 ANSWER 13 OF 14 TOXCENTER COPYRIGHT 2006 ACS on STN  
AN 2002:147486 TOXCENTER  
CP Copyright 2006 ACS  
DN CA13702015695B  
TI Acute effect of L-796568, a novel  $\beta$ 3-adrenergic receptor agonist, on  
energy expenditure in obese men  
AU Van Baak, Marleen A.; Hul, Gabby B. J.; Toubro, Soren; Astrup, Arne;  
Gottesdiener, Keith M.; DeSmet, Marina; Saris, Wim H. M.  
CS Nutrition and Toxicology Research Institute (NUTRIM), Maastricht  
University, Maastricht, 6200 MD, Neth..  
SO Clinical Pharmacology & Therapeutics (St. Louis, MO, United States),  
(2002) Vol. 71, No. 4, pp. 272-279.  
CODEN: CLPTAT. ISSN: 0009-9236.  
CY NETHERLANDS  
DT Journal  
FS CAPLUS  
OS CAPLUS 2002:363839  
LA English  
ED Entered STN: 2 Jul 2002  
Last Updated on STN: 2 May 2006

AB Our objective was to investigate the thermogenic efficacy of single oral  
doses of the novel  $\beta$ 3-adrenergic receptor agonist L-796568  
[(R)-N-[4-[2-[[2-hydroxy-2-(3-pyridinyl) ethyl]amino]ethyl]-phenyl]  
-4-[4-[4-(trifluoromethyl)phenyl] thiazol-2-yl]-benzenesulfonamide,  
dihydrochloride] in humans. Twelve healthy overweight to obese  
men participated in this 2-center, 3-period, randomized,  
placebo-controlled, crossover trial. In each period subjects received 250  
mg L-796568, 1000 mg L-796568, or placebo. Energy expenditure and RQ were  
determined by indirect calorimetry; blood samples were taken; and ear  
temperature,  
heart rate, and blood pressure were measured at baseline and during the  
4-h period after administration. Energy expenditure increased  
significantly after the 1000-mg dose (about 8%) and this was accompanied  
by an increase in plasma glycerol and free fatty acid concns. Systolic  
blood pressure also increased significantly. No changes in heart rate,  
diastolic blood pressure, ear temperature, plasma catecholamine, potassium, or  
leptin were found. Single-dose administration of 1000 mg of the novel  
 $\beta$ 3-adrenergic receptor agonist L-796568 increased lipolysis and  
energy expenditure in overweight men. This is the first study to show  
such an effect of  $\beta$ 3-adrenergic receptor agonists in humans without  
significant evidence for  $\beta$ 2-adrenergic receptor involvement.

TI Acute effect of L-796568, a novel  $\beta$ 3-adrenergic receptor agonist, on  
energy expenditure in obese men

AB . . . oral doses of the novel  $\beta$ 3-adrenergic receptor agonist L-796568  
[(R)-N-[4-[2-[[2-hydroxy-2-(3-pyridinyl) ethyl]amino]ethyl]-phenyl]  
-4-[4-[4-(trifluoromethyl)phenyl] thiazol-2-yl]-benzenesulfonamide,  
dihydrochloride] in humans. Twelve healthy overweight to obese  
men participated in this 2-center, 3-period, randomized,  
placebo-controlled, crossover trial. In each period subjects received 250  
mg L-796568, 1000 mg.

ST Miscellaneous Descriptors  
L796568 adrenoceptor agonist antiobesity energy expenditure lipolysis  
thermogenesis obesity

RN 211031-81-1 (L 796568)  
56-81-5 (Glycerol)

L9 ANSWER 14 OF 14 USPATFULL on STN

*dupl*



AN 2000:1891 USPATFULL  
 TI Thiazole benzenesulfonamides as  $\beta 3$  agonists for treatment of diabetes and obesity  
 IN Mathvink, Robert J., Red Bank, NJ, United States  
 Parmee, Emma R., Highland Park, NJ, United States  
 Tolman, Samuel, Jersey City, NJ, United States  
 Weber, Ann E., Scotch Plains, NJ, United States  
 PA Merck & Co., Inc., Rahway, NJ, United States (U.S. corporation)  
 PI US 6011048 20000104  
 AI US 1998-7363 19980115 (9)  
 PRAI US 1997-36760P 19970128 (60)  
 DT Utility  
 FS Granted  
 EXNAM Primary Examiner: Fan, Jane  
 LREP Yang, Mollie M., Rose, David L.  
 CLMN Number of Claims: 10  
 ECL Exemplary Claim: 1  
 DRWN No Drawings  
 LN.CNT 1510

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB Thiazole substituted benzenesulfonamides are  $\beta$ .sub.3 adrenergic receptor agonists with very little  $\beta$ .sub.1 and  $\beta$ .sub.2 adrenergic receptor activity and as such the compounds are capable of increasing lipolysis and energy expenditure in cells. The compounds thus have potent activity in the treatment of Type II diabetes and obesity. The compounds can also be used to lower triglyceride levels and cholesterol levels or raise high density lipoprotein levels or to decrease gut motility. In addition, the compounds can be used to reduced neurogenic inflammation or as antidepressant agents. The compounds are prepared by coupling an aminoalkylphenyl-sulfonamide with an appropriately substituted epoxide. Compositions and methods for the use of the compounds in the treatment of diabetes and obesity and for lowering triglyceride levels and cholesterol levels or raising high density lipoprotein levels or for decreasing gut motility are also disclosed.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

TI Thiazole benzenesulfonamides as  $\beta 3$  agonists for treatment of diabetes and obesity  
 AB . . . lipolysis and energy expenditure in cells. The compounds thus have potent activity in the treatment of Type II diabetes and obesity. The compounds can also be used to lower triglyceride levels and cholesterol levels or raise high density lipoprotein levels or. . . with an appropriately substituted epoxide. Compositions and methods for the use of the compounds in the treatment of diabetes and obesity and for lowering triglyceride levels and cholesterol levels or raising high density lipoprotein levels or for decreasing gut motility are. . .  
 SUMM . . . present invention are useful in treating or preventing include, but are not limited to, (1) diabetes mellitus, (2) hyperglycemia, (3) obesity, (4) hyperlipidemia, (5) hypertriglyceridemia, (6) hypercholesterolemia, (7) atherosclerosis of coronary, cerebrovascular and peripheral arteries, (8) gastrointestinal disorders including peptid ulcer, . . .  
 SUMM When treating obesity (in conjunction with diabetes and/or hyperglycemia, or alone) in human or non-human animals such as dogs and cats, generally satisfactory. . .  
 CLM What is claimed is:  
 9. A composition for the treatment of diabetes or obesity or for lowering triglyceride or cholesterol levels or increasing high density lipoprotein levels or for decreasing gut motility or for. . .  
 IT 211030-99-8P 211031-01-5P 211031-03-7P 211031-05-9P 211031-07-1P  
 211031-09-3P 211031-11-7P 211031-13-9P 211031-15-1P 211031-17-3P  
 211031-19-5P 211031-21-9P 211031-23-1P 211031-25-3P 211031-27-5P

211031-29-7P	211031-31-1P	211031-33-3P	211031-35-5P	211031-37-7P
211031-39-9P	211031-41-3P	211031-43-5P	211031-45-7P	211031-47-9P
211031-49-1P	211031-51-5P	211031-53-7P	211031-55-9P	211031-57-1P
211031-59-3P	211031-61-7P	211031-63-9P	211031-65-1P	211031-67-3P
211031-69-5P	211031-71-9P	211031-73-1P	211031-75-3P	211031-77-5P
211031-79-7P	211031-81-1P	211031-83-3P	211031-85-5P	
211032-15-4P	211032-17-6P	211032-19-8P	211032-21-2P	211032-23-4P
211032-25-6P	211032-27-8P	211032-29-0P	211032-31-4P	211032-33-6P
211032-35-8P	211032-37-0P	211032-39-2P	211032-41-6P	211032-43-8P
211032-45-0P	211032-47-2P	211032-49-4P	211032-51-8P	211032-53-0P
211032-55-2P	211032-57-4P	211032-59-6P	211032-61-0P	211032-64-3P
211032-67-6P	211032-70-1P	211032-73-4P	211032-75-6P	211032-78-9P
211032-81-4P	211032-84-7P	211032-87-0P	211032-89-2P	211032-91-6P
211032-93-8P	211032-95-0P	211032-97-2P	211033-00-0P	211033-03-3P
211033-05-5P				

(preparation of thiazole benzenesulfonamides as  $\beta 3$  agonists)

=>